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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner.

Case IPR2017-01987
Patent 8,911,737 B2

Before SUSAN L. C. MITCHELL, MICHELLE N. ANKENBRAND, and JACQUELINE T. HARLOW, *Administrative Patent Judges*.

ANKENBRAND, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Sandoz Inc. ("Petitioner") requests an *inter partes* review of claims 1–6 of U.S. Patent No. 8,911,737 B2 ("the '737 patent," Ex. 1001). Paper 1 ("Pet."). AbbVie Biotechnology Ltd. ("Patent Owner") filed a Preliminary Response. Paper 14 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b); 37 C.F.R. § 42.4(a). We may not institute an *inter partes* review "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Applying that standard, and upon consideration of the information presented in the Petition and the Preliminary Response, we deny the Petition and do not institute an *inter partes* review.[1]

II. BACKGROUND

A. Related Litigation

The parties do not identify any litigation or other Office proceedings involving the '737 patent. *See* Pet. 4–5; Paper 8, 1. Petitioner identifies litigation involving a patent that is related to the '737 patent, captioned *AbbVie Inc. v. Boehringer Ingelheim International GMBH*, No. 1:17-cv-01065 (D. Del. Aug. 2, 2017). Pet. 4–5.

B. Related Board Proceedings

Patent Owner explains that the '737 patent was filed as U.S. Patent Application No. 14/256,886, which is a divisional of U.S. Patent Application

[1] Because we deny the Petition, we dismiss as moot Petitioner's pending motions for Daniel L. Reisner and Abigail Langsam to appear *pro hac vice* in this proceeding (Papers 3 and 11, respectively).

No. 10/163,657, which issued as U.S. Patent No. 8,889,135 ("the '135 patent"). Paper 8, 1. Petitioner and Patent Owner identify three *inter partes* review proceedings involving the '135 patent: (1) *Coherus BioSciences Inc. v. AbbVie Biotechnology Ltd.*, Case IPR2016-00172 ("Coherus IPR"); (2) *Boehringer Ingelheim International GmbH v. AbbVie Biotechnology Ltd.*, Case IPR2016-00408 ("408 IPR"); and (3) *Boehringer Ingelheim International GmbH v. AbbVie Biotechnology Ltd.*, Case IPR2016-00409 ("409 IPR").[2] Pet. 5–6; Paper 8, 2. The Board issued Final Written Decisions in all three proceedings finding all claims of the '135 patent unpatentable as obvious. Coherus IPR, slip op. at 44 (PTAB May 16, 2017) (Paper 60) ("Coherus Final Dec."); 408 IPR, slip op. at 44 (PTAB July 6, 2017) (Paper 46) ("408 Final Dec."); 409 IPR, slip op. at 49 (PTAB July 6, 2017) (Paper 46) ("409 Final Dec.").

Petitioner identifies two additional *inter partes* review proceedings involving patents related to the '135 patent, in which the Board found the challenged claims unpatentable as obvious. Pet. 5–6.

C. The '737 Patent

The '737 patent, titled "Methods of Administering Anti-TNFα Antibodies," issued on December 16, 2014. Ex. 1001, (45), (54). According to the '737 patent, TNFα is a cytokine implicated in the pathophysiology of various diseases and disorders in humans, including rheumatoid arthritis ("RA") and inflammatory bowel disease ("IBD"), which includes Crohn's disease and ulcerative colitis. *Id.* at 1:15–30, 25:35–40, 27:12–24. Thus,

[2] We refer to the 408 IPR and the 409 IPR collectively as the "Boehringer IPRs."

TNFα is a target for various therapeutic strategies, including antibodies that bind to and neutralize TNFα, to inhibit its activity. *Id.* at 1:31–35, 24:51–64.

Several types of antibodies that bind and neutralize TNFα were known, including monoclonal antibodies prepared from mouse lymphocytes, chimeric antibodies that are part murine-derived and part human-derived, human monoclonal autoantibodies, and recombinant human antibodies. *Id.* at 1:35–2:51. Typical protocols for administering such antibodies, however, used intravenous administration on a weekly basis, which both have limitations. *Id.* at 2:51–57.

The '737 patent discloses methods for treating TNFα associated disorders by administering an anti-TNFα antibody subcutaneously every 13–15 days, i.e., biweekly. *E.g., id.* at 2:61–63, 3:42–52, 24:27–33. According to the '737 patent, biweekly dosing "has many advantages over weekly dosing," including a lower number of total injections and increased patient compliance, and subcutaneous dosing is advantageous to intravenous dosing because the patient can self-administer the antibody therapy. *Id.* at 2:63–3:5. The '737 patent also discloses that D2E7, a known recombinant human anti-TNFα antibody, is the most preferable antibody to use in the described methods. *Id.* at 3:31–41, 4:43–58, 9:65–10:5.

D. Illustrative Claim

Of the challenged claims, claim 1 is independent and illustrative of the claimed subject matter. Claim 1 recites:

> 1. A method for treating Crohn's disease in a human subject, comprising administering subcutaneously to a human subject having Crohn's disease a total body dose of 40 mg of a human anti-TNFα antibody once every 13–15 days for a time period sufficient to treat the Crohn's disease, wherein the anti-TNFα antibody comprises an IgG1 heavy chain constant region; a

> variable light ("V_L") chain region comprising a CDRl having the amino acid sequence of SEQ ID NO:7, a CDR2 having the amino acid sequence of SEQ ID NO:5, and a CDR3 having the amino acid sequence of SEQ ID NO:3; and a variable heavy ("V_H") chain region comprising a CDRl having the amino acid sequence of SEQ ID NO:8, a CDR2 having the amino acid sequence of SEQ ID NO:6 and a CDR3 having the amino acid sequence of SEQ ID NO:4.

Ex. 1001, 45:37–50.

E. The Asserted Grounds of Unpatentability

Petitioner asserts claims 1–6 of the '737 patent are unpatentable based on the following grounds:

References	Statutory Basis	Claims Challenged
Kempeni,[3] VDP1999,[4] Salfeld,[5] and Sandborn[6]	§103	1–6
VDP2000,[7] Rau,[8] Salfeld, and Sandborn	§103	1–6

[3] Joachim Kempeni, *Preliminary results of early clinical trials with the fully human anti-TNFα monoclonal antibody D2E7*, 58 ANN. RHEUM. DIS. 170–72 (1999) (Ex. 1004).
[4] L.B.A. van de Putte et al., *Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 42 ARTHRITIS & RHEUM. S400 (1999) (Ex. 1003).
[5] Salfeld et al., WO 97/29131, published Aug. 14, 1997 (Ex. 1006).
[6] William J. Sandborn & Stephen B. Hanauer, *Antitumor Necrosis Factor Therapy for Inflammatory Bowel Disease: A Review of Agents, Pharmacology, Clinical Results, and Safety*, 5 INFLAMMATORY BOWEL DISEASES 119–133 (1999) (Ex. 1005).
[7] L.B.A. van de Putte et al., *Six Month Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 59 ANNALS OF THE RHEUMATIC DISEASES OP.056 (2000) (Ex. 1107).
[8] R. Rau et al., *Experience with D2E7*, 25 RHEUMATOLOGY TODAY 83–88 (2000) (English translation, Ex. 1017).

Petitioner supports the Petition with the testimony of Simon Helfgott, M.D. (Ex. 1002), Ingvar Bjarnason, M.D. (Ex. 1008), and John Posner, Ph.D. (Ex. 1015).

F. The Coherus IPR and Boehringer IPRs

As we explain above, the Board previously considered the patentability of all claims of the ’135 patent in the Coherus IPR and the Boehringer IPRs. In the Coherus IPR, the Board determined that the claims of the ’135 patent were unpatentable because the subject matter of those claims would have been obvious over the combined teachings of Kempeni and VDP1999. *See* Coherus Final Dec. 44. In the Boehringer IPRs, the Board determined that the claims of the ’135 patent were unpatentable because the subject matter of those claims would have been obvious over the combined teachings of: (1) VDP2000 and Rau (408 IPR); (2) VDP1999 and Kempeni (409 IPR); and (3) VDP1999 and other references that are not asserted in this proceeding. *See* 408 Final Dec. 2, 43–44; 409 Final Dec. 2, 45–46, 48–49.

As Petitioner notes, and Patent Owner does not dispute, the only difference between claim 1 of the ’737 patent and claim 1 of the ’135 patent “is that ‘Crohn’s disease’ is substituted for ‘RA.’” Pet. 2. In other words, claim 1 of the ’135 patent and claim 1 of the ’737 patent recite treating human subjects having either RA (the ’135 patent) or Crohn’s disease (the ’737 patent) by administering subcutaneously a total body dose of 40 mg of D2E7 once every 13–15 days for a time period sufficient to treat the RA or Crohn’s disease. *Compare* Ex. 1001, 45:38–51, *with* Coherus Final Dec. 4 (setting forth claim 1 of the ’135 patent).

Here, as a predicate to its contention that the claimed methods for treating Crohn's disease would have been obvious, Petitioner relies on the combined teachings of VDP1999 and Kempeni, or VDP2000 and Rau in arguing that it would have been obvious to treat RA by administering subcutaneously a total body dose of 40 mg of D2E7 once every 13–15 days for a time period sufficient to treat the RA. Pet. 25–26, 39–45, 48–53; Ex. 1002 ¶¶ 34, 35, 48–64; *see generally* Ex. 1015. Thus, the Coherus IPR and Boehringer IPRs are relevant to Petitioner's asserted grounds.

III. ANALYSIS

We organize our analysis into three sections. First, we discuss the level of ordinary skill in the art. Second, we turn to claim construction. Third, taking account of the information presented, we consider whether the Petition meets the threshold showing for instituting an *inter partes* review based on obviousness.

A. Level of Ordinary Skill in the Art

We consider the asserted grounds of unpatentability in view of the understanding of a person of ordinary skill in the art. Petitioner contends that, as of the June 8, 2001 priority date of the '737 patent, the level of ordinary skill in the art would include a person having the skill set of "a pharmacologist having experience with antibody drugs" and a person or persons having the skill sets of "physicians treating patients for Crohn's and RA given the known association between the[] two diseases." Pet. 14. Petitioner elaborates that the pharmacologist would have a Ph.D. in pharmacology, pharmacokinetics, or a related field and at least three years of experience working on the pharmacokinetics/pharmacodynamics of biologic drugs. *Id.* (citing Ex. 1015 ¶ 33). And Petitioner explains that the

physicians each would have an M.D. and at least three years of post-residency experience treating patients for IBD and RA, respectively, including with anti-TNFα drugs. *Id.* (citing Ex. 1002 ¶ 26; Ex. 1008 ¶¶ 22–24).

Petitioner asserts that Dr. Bjarnason, Dr. Helfgott, and Dr. Posner are all "qualified to provide opinions as to what a [person of ordinary skill in the art] would have understood, known, or concluded from the prior art in their respective fields and are therefore competent to testify in this proceeding." *Id.* at 9–10 (citing Ex. 1002 ¶¶ 3–26; Ex. 1008 ¶¶ 3–10, 19–25; Ex. 1015 ¶¶ 3–16, 31–35). With respect to Dr. Helfgott, Petitioner explains that he "is an expert in the field of rheumatology." *Id.* at 9.

Patent Owner disputes that Dr. Helfgott is a person of ordinary skill in the art. Prelim. Resp. 24. In particular, Patent Owner asserts that because the claims of the '737 patent are directed to treating Crohn's disease, a person of ordinary skill in the art "would have the skill set[] of a physician treating Crohn's disease," and would not include a physician treating RA, such as Dr. Helfgott. *Id.* at 23–24 (citing *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1257 (Fed. Cir. 2007)).

At this stage of the proceeding, we agree with Patent Owner that a physician of ordinary skill in the art would have the skill set associated with treating Crohn's disease, which is not the field within which Dr. Helfgott's expertise lies. Dr. Bjarnason, a physician treating Crohn's disease, however, relies on and incorporates Dr. Helfgott's opinions regarding the obviousness of a 40 mg total dose of D2E7 administered subcutaneously every 13–15 days to treat RA (*see, e.g.*, Ex. 1008 ¶¶ 29, 109–110), and the prior art of record indicates that physicians investigating anti-TNFα therapy for treating

IBD (Crohn's disease and ulcerative colitis) also would have reviewed how the same therapy had been used to treat RA. *See, e.g.*, Ex. 1005, 119 (reviewing the use of anti-TNFα agents "for patients with IBD and [RA]"). Accordingly, on this record, we find Dr. Bjarnason's reliance on, and incorporation of, Dr. Helfgott's opinion testimony to be proper. *See* Federal Rule of Evidence 703 (providing that "[a]n expert may base an opinion on facts or data in the case that the expert has been made aware of"). We also find, for purposes of this decision, that the prior art itself is sufficient to demonstrate the level of ordinary skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that the prior art, itself, can reflect the appropriate level of ordinary skill in art).

B. Claim Construction

The Board interprets claims in an unexpired patent using the "broadest reasonable construction in light of the specification of the patent." 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, claim terms are given their ordinary and customary meaning in view of the specification, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner proposes two phrases for construction, both of which appear in claim 1: (1) the preamble, which recites a "method for treating Crohn's disease in a human subject"; and (2) "for a time period sufficient to treat Crohn's disease." Pet. 15. Petitioner argues that the preamble of claim 1 is

a statement of intended use and, therefore, is non-limiting. *Id.* Petitioner represents that its proffered construction is consistent with the Board's construction of the same preamble phrase for RA as non-limiting in the Coherus IPR. *Id.* (citing Coherus Final Dec. 6).

Regarding the phrase "for a time period sufficient to treat Crohn's disease," Petitioner, again, directs us to the Coherus IPR and the Boehringer IPRs, in which the Board determined that the phrase "for a time period sufficient to treat RA" does not require a specific level of efficacy. *Id.*; *see, e.g.*, Coherus Final Dec. 7–9. Petitioner proposes that, similar to the Coherus IPR and Boehringer IPRs, we construe the phrase "for a time period sufficient to treat Crohn's disease" to mean "for a time period sufficient to reduce the signs and/or symptoms of Crohn's disease." Pet. 15.

Patent Owner contends that it is not necessary for us to construe any claim terms to resolve the parties' dispute at this stage of the proceeding. Prelim. Resp. 7. We recognize that Petitioner's proposed constructions are consistent with the constructions the Board adopted in the Coherus IPR and Boehringer IPRs; however, because neither of those phrases requires construction for us to resolve the instant dispute, we decline to construe them. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("only those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy").

C. Petitioner's Asserted Obviousness Grounds

Petitioner asserts that claims 1–6 of the '737 patent are unpatentable under 35 U.S.C. § 103(a) because the subject matter of those claims would have been obvious over the combined teachings of: (1) Kempeni, VDP1999, Salfeld, and Sandborn; and (2) VDP2000, Rau, Salfeld, and Sandborn. Pet.

25–57. Patent Owner opposes. Prelim. Resp. 25–54. Having considered the arguments and evidence before us, for the reasons set forth below, we find that Petitioner does not establish a reasonable likelihood of prevailing on its asserted grounds.

1. Kempeni

Kempeni teaches that D2E7 is a fully human anti-TNFα monoclonal antibody that "may have advantages in minimising antigenicity in humans" compared to other biologic TNF antagonists that are not fully human or artificially fused human sequences. Ex. 1004, 170. Kempeni further describes the results of several clinical studies investigating the use of D2E7 to treat RA patients. *Id.* at 170–172.

In the first described study, each patient received a single dose of D2E7 (from 0.5 to 10 mg/kg)[9] or placebo by intravenous injection. *Id.* at 171. Patients were evaluated for four weeks to determine the pharmacokinetics of D2E7, and to evaluate the safety and efficacy of the antibody in terms of onset, duration, and magnitude of response. *Id.*

Kempeni describes the results of the study as "encouraging," noting that the "therapeutic effects became evident within 24 hours to one week after D2E7 administration and reached the maximum effect after 1–2 weeks, with dose response reaching a plateau at 1 mg/kg D2E7." *Id.* Pharmacokinetic parameters were calculated for patients from all dose groups and the estimated mean terminal half-life of D2E7 was determined to be 11.6 to 13.7 days. *Id.*

[9] The 0.5 to 10 mg/kg refers to the amount of D2E7 that patients received per kilogram of body weight.

Patients who continued in the study were given a second blinded dose that was identical to the first and, subsequently, given active drug every two weeks until a "good" response was achieved. *Id.* Kempeni discloses that 86% of patients continued to receive treatment with D2E7 after six months, "indicating that long term intravenous treatment with D2E7 in the dose range from 0.5 to 10 mg/kg was well tolerated." *Id.*

In a second study that evaluated the safety and efficacy of weekly subcutaneous 0.5 mg/kg weight-based administration of D2E7, patients were given either D2E7 or placebo weekly for a period of three months. *Id.* at 171–172. According to the preliminary data, "plasma concentrations of D2E7 after multiple subcutaneous doses were comparable to those achieved with intravenous administration." *Id.* at 172. Kempeni concludes that "D2E7 given subcutaneously was safe and as effective as when administered intravenously demonstrating that subcutaneous self administration is a promising approach for D2E7 delivery." *Id.*

In a third clinical study that evaluated the safety of 1 mg/kg single subcutaneous or intravenous injections, it was determined that the safety profile of single dose D2E7 administration was "comparable to that of placebo." *Id.*

Kempeni teaches the data from these studies collectively suggest that D2E7 "is safe and effective as monotherapy . . . when administered by single and multiple intravenous and subcutaneous injections. Additional studies are underway to further define optimal use of this novel treatment." *Id.*

2. VDP1999

VDP1999 is an abstract describing a dose-finding phase II study comparing three dose levels of D2E7 administered to patients with long-

standing active RA. Ex. 1003, 3.[10] The patients received weekly, fixed doses of either D2E7 at 20, 40, or 80 mg, or placebo by subcutaneous injection for three months. *Id.* VDP1999 concludes that "all doses of D2E7 were statistically significantly superior to placebo" and that "20, 40, and 80 mg/week were nearly equally efficacious when given [subcutaneously] in patients with active RA." *Id.*

3. VDP2000

VDP2000 describes an extension of the study set forth in VDP1999. Ex. 1107, 2.[11] After month three of the study, placebo-treated patients were switched to a weekly, fixed dose of 40 mg D2E7, while the other doses were continued as randomized (i.e., patients received weekly, fixed doses of 20 mg, 40 mg, or 80 mg D2E7). Like VDP1999, VDP2000 concludes that "all doses of D2E7 were statistically significantly superior to placebo" and that "20, 40, and 80 mg/week were nearly equally efficacious when given [subcutaneously] in patients with active RA." *Id.* VDP2000 further reports that "[t]he treatment benefit was stable for all parameters over time." *Id.*

4. Rau

Rau describes several clinical trials using D2E7 to treat RA. *See generally* Ex. 1017. After setting forth the details of the clinical trials and results obtained, Rau concludes:

> In summary, it can be established that the completely human TNFα antibody D2E7 is quickly (within the space of days) effective in the majority of patients, and has not lost its efficacy in the course of long-term treatment over, up to now, two and one-half years. D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection

[10] Our citations are to the page numbers Petitioner added to the exhibit.
[11] Our citations are to the page numbers Petitioner added to the exhibit.

> over 3–5 minutes or subcutaneously. D2E7 is well tolerated and must be called a clinical step forward.

Id. at 87.

5. Salfeld

Salfeld discloses the D2E7 antibody. *See* Ex. 1006, 3:19–24, 12:5–9. Salfeld generally describes incorporating the antibody or antibody-portions into pharmaceutical compositions suitable for subcutaneous administration. *See id.* at 27:20–21, 28:4–6, 7–8. Salfeld identifies a dosage range of 0.1–20 mg/kg. *Id.* at 33:31–33. Salfeld explains that TNF has been implicated in the pathophysiology of both RA and IBD, and that D2E7 can be used to treat both RA and IBD, including Crohn's disease and ulcerative colitis. *Id.* at 36:34–37:15, 39:15–23.

6. Sandborn

Sandborn is a clinical review describing the use of anti-TNFα agents infliximab (a chimeric monoclonal antibody), CDP571 (a humanized monoclonal antibody), and etanercept (a human recombinant fusion protein) in studies treating patients with IBD (Crohn's disease and ulcerative colitis) and RA. Ex. 1005, 119. Sandborn first summarizes several clinical studies aimed at treating patients with Crohn's disease. Sandborn reports that patients with Crohn's disease who received doses of 5 mg/kg, 10 mg/kg, or 20 mg/kg infliximab administered as a single intravenous infusion or repeated infusions (e.g., dosing at weeks 0, 2, and 6) showed improvement and remission, with a dose of 5mg/kg determined as "the best dose for both improvement and induction of clinical remission." *Id.* at 125–126, Table 2. In one study, patients who responded to an initial dose of infliximab were re-randomized after 12 weeks to treatment with placebo or 10 mg/kg infliximab at weeks 12, 20, 28, and 36, and followed through 48 weeks. *Id.* at 126–127.

Sandborn reports that the results "were not definitive," but suggest that infliximab may be effective for maintaining remission for patients who respond to an initial infusion. *Id.* at 127.

For CPD571, Sandborn describes one study in which patients received a single dose of placebo or 5 mg/kg CDP571 and were followed for 8 weeks. *Id.* The study results "suggested that 5 mg/kg CDP571 may have short-term efficacy" in CD, but "optimal dose and dosing interval . . . remain to be determined." *Id.*

Sandborn reports "there are no published clinical trials with etanercept for the treatment of [Crohn's disease]." *Id.*

Turning to RA, Sandborn describes multiple studies in which RA patients received infliximab, CDP571, or etanercept. *Id.* at 127–129. Sandborn reports that patients with RA showed clinical improvement after receiving a single infusion of 5 mg/kg, 10 mg/kg, or 20 mg/kg infliximab. "The clinical response to infliximab tended to be more durable for patients receiving the 10 mg/kg and 20 mg/kg doses." *Id.* at 127. Eleven patients from that study continued with an open label retreatment protocol in which they received three infusions of 10 mg/kg infliximab administered at weeks 12, 20, and 28. *Id.* at 127–128. The results of the two studies "demonstrated that infliximab at doses of 5 mg/kg, 10 mg/kg, and 20 mg/g was effective for active RA . . . and suggested that repeated dosing may be beneficial." *Id.* at 128.

Sandborn also describes two placebo-controlled, dose-ranging trials in which patients received multiple doses of placebo, 3 mg/kg infliximab, or 10 mg/kg of infliximab. *Id.* at 128. In the first study, patients received infusions at weeks 0, 2, 6, 10, and 14. The results "demonstrated that

repeated administration of infliximab at doses of 3 mg/kg [or] 10 mg/kg . . . was effective for inducing and maintaining a clinical response in active RA patients." *Id.* In the second study, patients received placebo, 3 mg/kg infliximab every 4 weeks, 3 mg/kg infliximab every 8 weeks, 10 mg/kg infliximab ever 4 weeks, 10 mg/kg infliximab every 8 weeks for a total of 30 weeks. *Id.* Sandborn observed that the results from the study "demonstrated that repeated administration of infliximab was effective for inducing and then maintaining a clinical response in active RA [patients]" and that 3 mg/kg of infliximab administered every 8 weeks "was the optimal therapeutic strategy." *Id.*

With respect to CDP571, Sandborn describes a study in which patients first received a single infusion of placebo or 0.1 mg/kg, 1 mg/kg, or 10 mg/kg CDP571 and were followed for 8 weeks. *Id.* at 128. Most of the patients entered a retreatment protocol consisting of a single dose of 1 mg/kg or 10 mg/kg and followed for an additional 8 weeks. Sandborn concludes that the study "provides preliminary evidence that CDP571 is efficacious for active RA and suggests a dose response." *Id.*

Sandborn describes four studies in which RA patients received subcutaneous injections of placebo or different doses of etanercept. *Id.* at 128–129. The studies found a number of different etanercept doses effective at treating RA, with twice-weekly doses of 25 mg etanercept the most effective. *Id.* at 129.

Sandborn also describes two preliminary studies in patients with ulcerative colitis—one using infliximab and one using CDP571. In the infliximab study, patients received a single dose of placebo or 5 mg/kg, 10 mg/kg, or 20 mg/kg of infliximab and were followed for 2 weeks.

Patients in all three dose groups achieved a clinical response, leading Sandborn to conclude that "infliximab may be of benefit in severe [ulcerative colitis], but additional studies are needed to prove efficacy and to determine optimal dose and dosing interval." *Id.* at 129. In the CDP571 study, patients received a single dose of 5 mg/kg CDP571 and followed for 8 weeks. *Id.* The study results suggested "a possible short-term benefit from CDP571, 5 mg/kg (up to 2 weeks)" in ulcerative colitis.

Sandborn further discloses that there were no published clinical trials of etanercept for treating ulcerative colitis. *Id.*

7. Analysis

We now turn to Petitioner's asserted grounds, focusing on independent claim 1. For the first asserted ground, based in-part on Kempeni and VDP1999, Petitioner points to the Board's findings in the Coherus IPR and 409 IPR that the collective teachings of those references would have rendered obvious a 40 mg fixed dose of D2E7 administered subcutaneously every 13–15 days to treat RA. Pet. 39–42 (citing Coherus Final Dec. 15–17, 25, 26). Petitioner also directs us to Dr. Posner's testimony reaching the same conclusions based on Kempeni and VDP1999's disclosures. *Id.* (citing Ex. 1015 ¶¶ 37–48, 65–68, 80–85, 99–103; Ex. 1003, 3; Ex. 1004, 171–172). For the second asserted ground, based in-part on VDP2000 and Rau, Petitioner, likewise, points to the Board's findings in the 408 IPR and Dr. Posner's testimony that the collective teachings of those references would have rendered obvious the same dosage regimen for treating RA. *Id.* at 48–53 (citing 408 Final Dec. 15, 17–18, 26–38, 44; Ex. 1015 ¶¶ 60, 63–64, 69–74, 94–95, 109–120).

For both asserted grounds, Petitioner argues that the "only difference" between claim 1 of the '737 patent and "claim 1 of the '135 patent invalidated by the Board, is that 'Crohn's disease' is substituted for 'RA.'" Pet. 2, 25. Petitioner further contends that Salfeld and Sandborn account for that difference because each reference "taught treating both Crohn's and RA by administering drugs, including TNF-α inhibitors, using the same dosing regimens." *Id.* at 2, 26–27, 45; *see id.* at 53 (applying the arguments made with respect to the first asserted ground regarding using the same dosing regimen to treat RA and Crohn's disease to the second asserted ground). In particular, Petitioner asserts that Salfeld discloses treating RA and Crohn's disease with the same D2E7 dosage range—0.1 mg/kg to 20 mg/kg. *Id.* at 3, 26–27 (citing Ex. 1006, 28:5, 33:31–33, 36:9–40:17[12]). Petitioner further points to the above-discussed studies from Sandborn as "confirm[ing] that TNF-α inhibitors were used to treat both RA and Crohn's using the same doses and dosing intervals." *Id.* at 28; *see id* at 27–34. Petitioner also relies on the disclosures in Salfeld and Sandborn to support its assertion that the person of ordinary skill in the art would have had a reason to treat Crohn's disease with the RA dosing regimen disclosed in the combined teachings of VDP1999 and Kempeni, or VDP2000 and Rau. *Id.* at 27, 45–46.

Petitioner contends that the combined teachings of VDP1999, Kempeni, Salfeld, and Sandborn, or VDP2000, Rau, Salfeld, and Sandborn would have provided the skilled artisan with a reasonable expectation of success in treating Crohn's disease by administering subcutaneously 40 mg

[12] Our citations to Exhibit 1006 in this decision are to the original page numbers on the reference, not to the page numbers that Petitioner added to the exhibit.

D2E7 every 13–15 days, based on: (1) VDP1999 and Kempeni's or VDP2000 and Rau's disclosure of the claimed dosing regimen, which the Board determined would have been obvious to treat RA; (2) Salfeld's teaching "that D2E7 could be subcutaneously administered to treat both RA and Crohn's [disease] within the same dosing range"; and (3) the prior art teachings that TNFα inhibitors were effective in treating both RA and Crohn's disease with the same dose and dosing regimen. *Id.* at 46–47 (citing Coherus Final Dec. generally; 409 Final Dec. generally; Ex. 1006, 33:31–33, 36:34–39:25; Ex. 1008 ¶¶ 68–100, 110–111; Ex. 1015 ¶¶ 65–74).[13] With respect to the prior art teachings that TNFα inhibitors could treat both RA and Crohn's disease, Petitioner relies primarily on Sandborn, which Petitioner summarizes as teaching that:

> (1) TNF-α is implicated in both RA and Crohn's [disease]; (2) the same drugs used to treat RA were generally used to treat Crohn's [disease] using the same or similar dosing regimens; and (3) the TNF-α inhibitor infliximab was known to be efficacious in the treatment of RA and Crohn's [disease] at the same doses and dosing regimens.

Id. at 46. Petitioner also contends that the applicants for the '737 patent "confirmed th[e] . . . expectation of success" because they "obtained the D2E7 Crohn's treatment claims . . . based solely upon data for treating RA with D2E7." *Id.* at 3.

Having considered the arguments and evidence, we are not persuaded that Petitioner shows a reasonable likelihood of prevailing in its assertion

[13] Petitioner also points to small molecule drugs that Petitioner contends were used to treat both RA and Crohn's disease at the same or similar doses and dosing regimens as supporting a reasonable expectation of success. Pet. 37–38. We find that evidence less relevant because those drugs are not biologic TNFα inhibitors.

that the subject matter of the '737 patent would have been obvious over the cited prior art. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does." *Id.* Moreover, a person of ordinary skill in the art must have had a reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014).

Even assuming, as Petitioner argues, that a skilled artisan would have had a reason to combine the teachings of VDP1999 and Kempeni, or VDP2000 and Rau, with those of Salfeld and Sandborn to treat patients having Crohn's disease with the claimed dosing regimen, we are not persuaded on this record that a skilled artisan would have had a reasonable expectation of success in doing so as of the June 8, 2001 priority date of the '737 patent. As explained above, Petitioner argues that a skilled artisan would have had a reasonable expectation that a dosing regimen that was effective in treating RA also would have been effective in treating Crohn's disease. Pet. 46.

In response, Patent Owner contends that although skilled artisans hypothesized that the same TNFα inhibitor could be administered at the same dose and dose frequency to treat both RA and Crohn's disease (i.e., an anti-TNFα class effect) based on early results reported in the art, later clinical study results did not support that hypothesis. Prelim. Resp. 2–3, 14–15, 37–39. For example, Patent Owner directs us to a May 2001 Sandborn reference that describes a clinical study conducted to determine the safety

and efficacy of etanercept for moderate to severe Crohn's disease. Ex. 2015, A-20.[14] Patients enrolled in the eight-week study received either placebo or etanercept using the same dose and dosing regimen already approved to treat RA—25 mg by twice-weekly subcutaneous administration. *Id.* Sandborn 2001 reported that clinical responses in patients who received etanercept were the same as those in patients who received placebo. *Id.* Those results led Sandborn 2001 to conclude that the dose of etanercept approved to treat RA "is not an effective therapy for patients with moderate to severe [Crohn's Disease]. . . . Higher doses or more frequent dosing may be required to attain a response in patients with active [Crohn's disease]." *Id.*

As the Federal Circuit has explained, "there can be little better evidence negating an expectation of success than actual reports of failure." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1081 (Fed. Cir. 2012) (citation and internal quotation marks omitted). Petitioner and Dr. Bjarnason do not address the finding in Sandborn 2001 that etanercept was ineffective at treating Crohn's disease when administered at the same dose using the same dosing regimen effective in RA patients, relying instead on statements in Sandborn (from May 1999) that there had been no published clinical trials of etanercept for IBD. Pet. 22 n.17; Ex. 1008 ¶ 38 n.2. Petitioner's assertion that a person of ordinary skill in the art "would readily understand . . . that a dose of a TNF-α inhibitor that is effective in treating RA would be expected to also be effective in treating

[14] William J. Sanborn et al., *A Randomized, Double-Blind, Placebo-Controlled Trial Of Subcutaneous Etanercept (p75 Soluble Tumor Necrosis Factor:FC Fusion Protein) In The Treatment Of Moderate To Severe Crohn's Disease*, 120 GASTROENTEROLOGY A-20 (2001) ("Sandborn 2001").

Crohn's [disease]" (Pet. 34 (citing Ex. 1008 ¶ 80)) is not persuasive in view of the etanercept study failure Sandborn 2001 reports—a study specifically designed to test whether the dose and dosing regimen of TNFα inhibitor etanercept effective to treat RA would also be effective to treat Crohn's disease. Ex. 2015, A-20.

Given the foregoing, Petitioner does not establish a reasonable likelihood of prevailing in its assertion that the subject matter of claim 1 would have been obvious over the combination of VDP1999, Kempeni, Salfeld, and Sandborn, or VDP2000, Rau, Salfeld, and Sandborn. Because dependent claims 2–6 also require treating Crohn's disease by administering subcutaneously 40 mg of D2E7 every 13–15 days, Petitioner also does not establish a reasonable likelihood of prevailing on its asserted grounds as to those claims.

IV. CONCLUSION

Taking account of the information presented in the Petition and the Preliminary Response, and the evidence of record, we determine that Petitioner fails to establish a reasonable likelihood of prevailing at trial as to any challenged claim. Accordingly, the Petition is *denied*, and we do not institute trial.

V. ORDER

It is hereby

ORDERED that the Petition is *denied* as to all challenged claims of the '737 patent, and no trial is instituted;

FURTHER ORDERED that Petitioner's *Pro Hac Vice* Motion to Admit Daniel L. Reisner Pursuant to 37 C.F.R. § 42.10(c) (Paper 3) is *dismissed as moot*; and

FURTHER ORDERED that Petitioner's *Pro Hac Vice* Motion to Admit Abigail Langsam Pursuant to 37 C.F.R. § 42.10(c) (Paper 11) is *dismissed as moot*.

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